

with the expensive 5-hydroxytryptamine₃ receptor antagonists, treatment of established postoperative nausea and vomiting is efficacious at much lower doses than are necessary for successful prophylaxis.¹⁰ If 30% of surgical patients suffer from postoperative nausea and vomiting,² and we assume that in about half of those symptoms are persisting, then the target population for prophylaxis is about 15%. These patients are suffering unnecessarily, they want their opioid analgesia to be stopped, and they may need overnight admission due to intractable vomiting. For those, further investigations are warranted. Valid data are needed on old molecules that are still widely used in clinical practice (for example, haloperidol or hyoscine).

Hopefully, new compounds that block yet another receptor system of the emesis pathways and that have shown promising results in animal models will further improve the treatment of postoperative nausea and vomiting.¹¹

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Merck, US, manufacturer of aprepitant. He has been invited to an international consensus meeting on postoperative nausea and vomiting (sponsored by Aventis, US), has received fees from lectures from MSD Switzerland and Pfizer Norway, and is a recipient of a PROSPER grant from the Swiss National Science Foundation (No 3233-051939.97/2).

- 1 Clergue F, Auroy Y, Pequignot F, Jouglé E, Lienhart A, Laxenaire MC. French survey of anaesthesia in 1996. *Anesthesiology* 1999;91:1509-20.
- 2 Tramèr MR. A rational approach to the control of postoperative nausea and vomiting: evidence from systematic reviews. Part I. Efficacy and harm of antiemetic interventions, and methodological issues. *Acta Anaesthesiol Scand* 2001;45:4-13.
- 3 VanWijk MGF, Smalhout B. A postoperative analysis of the patient's view of anaesthesia in a Netherlands' teaching hospital. *Anaesthesia* 1990;45:679-82.
- 4 Gan T, Sloan F, Dear G, El-Moalem HE, Lubarsky DA. How much are patients willing to pay to avoid postoperative nausea and vomiting? *Anesth Analg* 2001;92:393-400.
- 5 Tramèr MR, Reynolds DJM, Moore RA, McQuay HJ. Impact of covert duplicate publication on meta-analysis: a case study. *BMJ* 1997;315:635-40.
- 6 Stadler M, Bardiau F, Seidel L, Albert A, Boogaerts JG. Difference in risk factors for postoperative nausea and vomiting. *Anesthesiology* 2003;98:46-52.
- 7 Sweeney BP. Why does smoking protect against post operative nausea and vomiting? *Br J Anaesth* 2002;89:810-3.
- 8 Gan TJ, Meyer T, Apfel C, Chung F, Davis PJ, Eubanks S, et al. Consensus guidelines for the management of postoperative nausea and vomiting. *Anesth Analg* 2003;97:62-71.
- 9 Adriani J, Summers FW, Antony SO. Is the prophylactic use of antiemetics in surgical patients justified? *JAMA* 1961;175:666-71.
- 10 Kazemi-Kjellberg F, Henzi I, Tramèr MR. Treatment of established postoperative nausea and vomiting: a quantitative systematic review. *BMC Anesthesiol* 2001;1:2.
- 11 Gesztesi Z, Scuderi PE, White PF, Wright W, Wender RH, D'Angelo R, et al. Substance P (Neurokinin-1) antagonist prevents postoperative vomiting after abdominal hysterectomy procedures. *Anesthesiology* 2000;93:931-7.

Race, ethnic group, and clinical research

Implications of incorporating race and ethnicity into trials go beyond ethical issues

Since 1993 guidelines issued by the US National Institutes of Health (NIH) have mandated the proportionate representation of patients by race and ethnic group in clinical research funded by the NIH. No similar requirement exists in the United Kingdom, although concerns of low participation by minorities in randomised trials have led to calls for the adoption of a similar standard.¹ It is likely that the role of race in clinical research will also inevitably be addressed by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (www.ich.org) as part of its efforts to standardise clinical research in the United States, Europe, and Japan. Although ensuring equal opportunities for participation in randomised trials for members of all racial groups is ethical, we believe that the explicit consideration of race during enrolment in a randomised trial, and clinical research broadly, raises serious concerns.

A recent report describing the enrolment of South Asian patients in randomised controlled trials conducted at the University of Leeds extends previous work documenting the relatively low enrolment of racial and ethnic minorities in randomised trials in the United States.^{1 2} Although the findings of these studies merit further exploration, several important questions remain unresolved and thus preclude any definitive conclusions or interpretations of the findings. What

remains to be determined is the process by which the low enrolment rate is achieved. Authors have invariably invoked investigator bias, inappropriate strategies for recruitment, or cost issues due to translation,¹ but other more basic questions deserve consideration. Does this pattern represent confounding by centres such that centres with a higher prevalence of patients from minorities participate in randomised clinical trials—both in serving as centres and in recruitment rates—at disproportionately lower rates than centres with a lower prevalence of patients from minorities? Is the lower enrolment attributable to explicit eligibility criteria for the study—for example, the exclusion of patients with contraindications that are more prevalent in patients from a minority? Or is it due to confounding by other implicit selection factors, such as the exclusion of eligible patients who have marked comorbidity, that is more prevalent in patients from a minority group?

Are patients from minorities more likely to refuse to participate in randomised trials? Or, more worryingly, does the pattern represent a lower rate of offers to participate in randomised trials to patients from minorities compared with clinically comparable patients of other ethnic groups treated in the same centres? These hypotheses can be addressed readily by assessment of enrolment registries of studies. It is therefore disappointing that no such evaluation has yet

been conducted. Without knowing the answer to these questions we are left with descriptive reports that provide little insight into the processes accounting for this pattern.

Absent from this literature is a consensus on what proportion of patients from minorities in a randomised trial cohort constitutes the “right” prevalence. Do we base requirements on prevalence in the general population, as some have suggested?¹ Or do we instead choose disease or condition specific recruitment standards? If so, what standard(s)—incidence, prevalence, burden of disease, or outcomes? Alternatively if representation of racial or ethnic minorities is predicated on assessing the consistency of study findings across different groups, then considerations of the statistical power of subgroup analysis would imply oversampling of racial groups in order to enrol members of racial groups in equal proportions. Although it is not clear what requirement represents the optimal approach, each conveys notably different and potentially important implications for the enrolment of patients into randomised trials.

The stated rationale for ensuring adequate representation of ethnic minorities in randomised trials is also contentious. Ensuring representation of minorities in randomised trials to ensure that no patients are excluded from clinical research for inappropriate reasons is a valid ethical reason for assessing enrolment rates for racial or ethnic groups. However, the recruitment of patients from minorities into randomised trials is often advocated in order to conduct subgroup analyses based on race. The assumption underlying this goal is that race and ethnic group represent valid biological constructs that may modify the effect of any drug studied in a randomised trial and thus necessitate race specific treatments.³

Although the utility of employing race and ethnic group in medical research remains a source of considerable debate⁴⁻⁵ few would consider race to represent a unique biological factor that would modify the effect of any studied intervention. Instead race and ethnic group are assumed to serve as proxies for a mix of genetic, disease, social, behavioural, or clinical characteristics, which vary by group. However, relying on analyses stratified by race or ethnic group, rather than directly assessing the specific factor, which may instead be correlated with group membership, perpetuates pseudoscientific rationalisations of the fundamentally social concepts of race and ethnic group.⁶ No clearer example of this phenomenon exists than the lack of consistent labels or descriptions ascribed to racial groups.⁷

There are also more immediate consequences for formalising requirements for enrolment with regard to race and ethnic group in randomised trials. Any study that seeks to conduct analyses stratified by race and ethnicity appropriately must incorporate this objective

into its initial design.⁸ Adequately powered analyses of subgroups by race or ethnic group will necessitate a priori increases in study size to assess the same desired effect as a study not employing such subgroup analyses. Alternatively studies that are limited to recruiting a set number of patients will need to increase the predefined expected effect size in order to conduct race based subgroup analyses. Regardless of the response, incorporating race and ethnic group explicitly into the design of randomised trials will have clear implications for the costs, feasibility, and arguably results of these studies. These consequences bear consideration since initial reports of racial variations in therapeutic efficacy⁹⁻¹⁰ have not been supported in subsequent analyses.¹¹⁻¹²

The potential implications of incorporating race and ethnic group into randomised trials are numerous and deserving of further study and discussion. Rather than reflexively adopting policies concerning race and ethnic group and enrolment of subjects in randomised trials, the United Kingdom has the opportunity to begin a measured discussion of the objectives and implications for research of employing race and ethnic group in clinical research designs.

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- 1 Mason S, Hussain-Gambles M, Leese B, Atkin K, Brown J. Representation of South Asian people in randomised clinical trials: analysis of trials' data. *BMJ* 2003;326:1244-5.
- 2 Heiat A, Gross CP, Krumholz HM. Representation of the elderly, women, and minorities in heart failure clinical trials. *Arch Intern Med* 2002;162:1682-8.
- 3 Taylor AL, Cohn JN, Worcel M, Fraciosa JA. The African-American heart failure trial: background, rationale, and significance. *J Natl Med Assoc* 2002;94:762-9.
- 4 Burchard EG, Ziv E, Coyle N, Gomez SL, Tang H, Karter AJ, et al. The importance of race and ethnic background in biomedical research and clinical practice. *N Engl J Med* 2003;348:1170-5.
- 5 Cooper RS, Kaufman JS, Ward R. Race and genomics. *N Engl J Med* 2003;348:1166-70.
- 6 Schwartz RS. Racial profiling in medical research. *N Engl J Med* 2001;344:1392-3.
- 7 Aspinall PJ. Who is Asian? A category that remains contested in population and health research. *J Public Health Med* 2003;25:91-7.
- 8 Moye LA, Powell JH. Evaluation of ethnic minorities and gender effects in clinical trials: opportunities lost and rediscovered. *J Natl Med Assoc* 2001;93(Suppl):S29-34.
- 9 Exner DV, Dries DL, Domanski MJ, Cohn JN. Lesser response to angiotensin-converting-enzyme inhibitor therapy in black as compared with white patients with left ventricular dysfunction. *N Engl J Med* 2001;344:1351-7.
- 10 Weisberg LA. The efficacy and safety of ticlopidine and aspirin in non-whites: analysis of a patient subgroup from the Ticlopidine Aspirin Stroke Study. *Neurology* 1993;43:27-31.
- 11 Shekelle PG, Rich MW, Morton SC, Atkinson SW, Tu W, Maglione M, et al. Efficacy of angiotensin-converting enzyme inhibitors and beta-blockers in the management of left ventricular systolic dysfunction according to race, gender, and diabetic status: a meta-analysis of major clinical trials. *J Am Coll Cardiol* 2003;41:1529-38.
- 12 Gorelick PB, Richardson D, Keely M, Ruland S, Hung E, Harris Y, et al. Aspirin and ticlopidine for prevention of recurrent stroke in black patients: a randomized trial. *JAMA* 2003;289:2947-57.